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The influence of chiral auxiliaries and catalysts on the selectivity of intramolecular conjugate additions of pyrrole to *N*-tethered Michael acceptors

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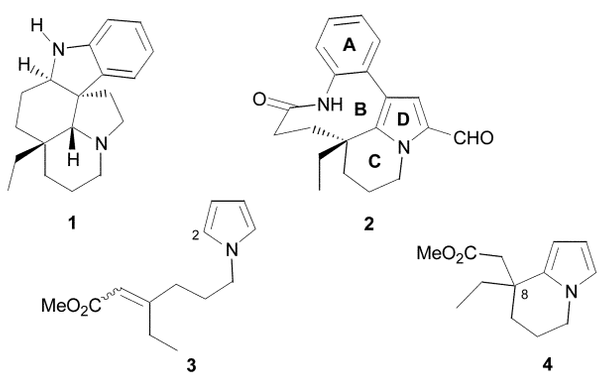
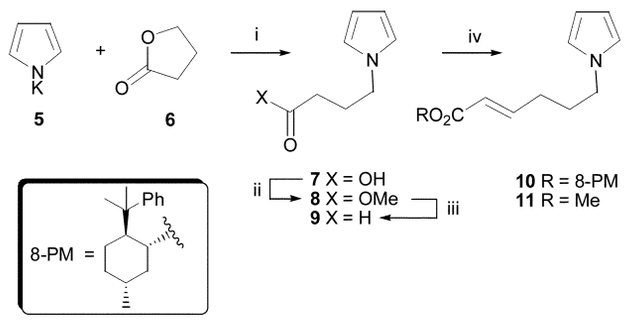
A series of pyrroles incorporating *N*-tethered acrylates and related groups has been prepared and examined for their capacity to undergo intramolecular Michael addition reactions to form, in a diastereo- or enantio-selective fashion, the corresponding 8-substituted tetrahydroindolizidine or homologues thereof.

A key step associated with our recently disclosed syntheses of the racemic modifications of the alkaloids aspidospermidine (**1**)[1] and rhazinal (**2**)[2] was the $AlCl_3$-catalysed Michael addition[3] of C2 within pyrrole **3** onto the *N*-tethered acrylate residue thus producing the tetrahydroindolizidine **4**. To the best of our knowledge, conversion **3**⟶**4** represents the first example of an intramolecular variant of a rather well-known intermolecular process.[4] Of course, the utility of this variant would be greatly enhanced if it could be achieved in an enantioselective fashion. To this end we have examined the capacity of certain chiral catalysts and auxiliaries to effect asymmetric induction in the title processes and report the results of our studies here.

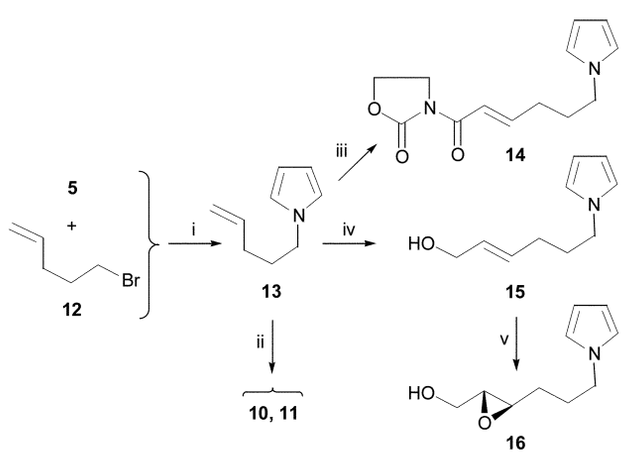


The substrates required for our study were initially generated (Scheme 1) by simple variations on the originally described[2] route to the "parent system" **3**. Thus, reaction of the potassium salt of pyrrole (**5**) with γ-butyrolactone **6** gave, after acidic work up, the previously reported[1,2] acid **7** (95%). The readily derived methyl ester **8** was reduced, with DIBAL-H, to the unstable aldehyde **9** which was subjected to *in situ* Wadsworth–Horner–Emmons-type olefination with the relevant phosphonoacetate[5] thus affording the required substrates **10** (68% from **8**, 4 : 1 mixture of *E*- and *Z*-isomers) and **11** (79% from **8**, 10 : 1 mixture of *E*- and *Z*-isomers).

An alternate and more expeditious route to compounds **10** and **11** involved (Scheme 2) *N*-alkylation of pyrrole with 5-bromo-1-pentene (**12**) and then subjecting the product alkene **13** (84%) to an olefin cross metathesis (OCM)[6] with the relevant



Scheme 1 *Reagents and conditions*: (i) 160 °C, 12 h; (ii) CH_2N_2 (excess), Et_2O, 18 °C, 3 h; (iii) DIBAL-H (1.0 mole eq.), THF, −78 °C, 1 h; (iv) (a) for **10**: $(MeO)_2P(O)CH_2CO_2$8-PM (1.1 mole eq.), LiHMDS, CH_2Cl_2, 18 °C, 1 h; (b) for **11**: $(MeO)_2P(O)CH_2CO_2Me$ (1.1 mole eq.), KHMDS, CH_2Cl_2, 18 °C, 1 h.



Scheme 2 *Reagents and conditions*: (i) KH (2.0 mole eq.), THF, 18 °C, 16 h; (ii) (a) for **10**: CH_2=$CHCO_2$8-PM (1.1 mole eq.), Grubbs' 2nd gen. catalyst (5 mole%), CH_2Cl_2, 40 °C, 24 h; (b) for **11**: CH_2=$CHCO_2Me$ (1.1 mole eq.), Grubbs' 2nd gen. catalyst (5 mole%), CH_2Cl_2, 40 °C, 24 h; (iii) *N*-acryloyl oxazolidinone (1.0 mole eq.), Grubbs' 2nd gen. catalyst (10 mole%), CH_2Cl_2, 40 °C, 24 h; (iv) $TBSOCH_2CH$=CH_2OTBS (2.0 mole eq.), Grubbs' 1st gen. catalyst (10 mole%), CH_2Cl_2, 40 °C, 24 h then TBAF (1.2 mole eq.), THF, 18 °C, 2 h; (v) *t*-BuOOH (1.0 mole eq.), $Ti(O\textit{i}\text{–}Pr)_4$ (1.0 mole eq.), diisopropyl (+)-tartrate (1.0 mole eq.), 4 Å molecular sieves, CH_2Cl_2, −20 °C, 24 h.

acrylate[7] in the presence of Grubbs' 2nd generation catalyst.[8] The latter step of these simple sequences was efficient (> 75%) and proceeded with high *E*-selectivity such that serviceable quantities of the target substrates could be obtained in just a few steps from readily available starting materials. Simple extensions of this approach provided cyclisation precursor **14** (83%, *E*-isomer only) and allylic alcohol **15** (76%, 8.5 : 1 mixture of *E*- and *Z*-isomers). Subjection of the latter compound to Sharpless asymmetric epoxidation (SAE)[9] using diisopropyl (+)-tartrate afforded epoxy-alcohol **16** (87%, 98% ee[10]) as

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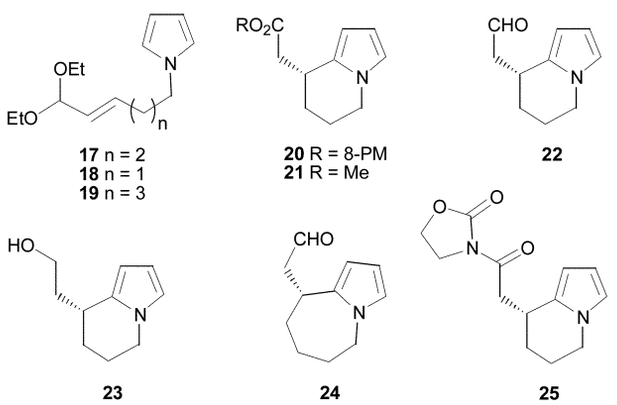
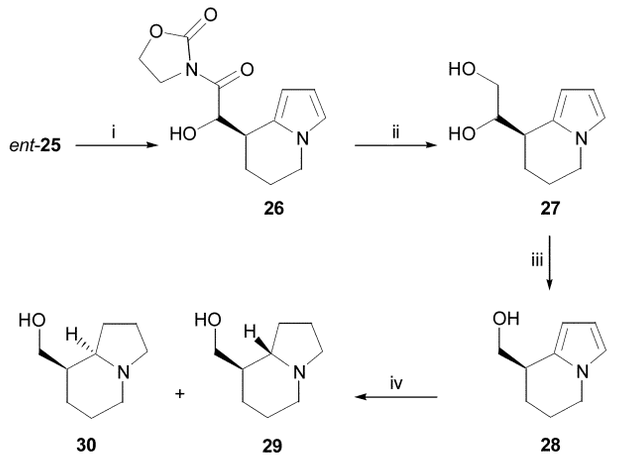
another potential cyclisation substrate. An OCM reaction involving alkene **13** and acrolein diethyl acetal[11] afforded product **17** (75% of a 4 : 1 mixture of *E*- and *Z*-isomers). Analogous treatment of the same precursor acetal with the readily available lower and higher homologues of alkene **13** afforded the lower and higher homologues of **17**, *i.e.* **18** and **19** respectively, in essentially the same yields and *E*/*Z* ratios. Compounds **17**–**19** proved to be very unstable materials and were, therefore, immediately subjected to the cyclisation reactions described below.

Preliminary cyclisation studies were undertaken with the (−)-8-phenylmethyl ester *E*-**10** which reacted with boron trifluoride diethyl etherate in DCM at −20 °C to give the expected product **20** in 82% yield and 90% de as judged by 500 MHz ^{1}H NMR analysis. Reaction of methyl ester *E*-**11** under analogous conditions gave (±)-**21** in 95% yield. The initial assignment of the *R*-configuration at C8 to the major diastereoisomeric form of **20** followed from consideration of transition state structures[12] and was confirmed by chemical correlation studies (*vide infra*). Reaction of the unsaturated acetal **17** with MacMillan's organocatalyst[13] in THF–water at −20 °C for 24 h afforded the expected aldehyde **22** in 83% yield and 87% ee as determined by chiral HPLC analysis of the derived alcohol **23**.[14] That the sense of the asymmetric induction associated with the conversion **17**⟶**22** is the same as obtained for the preceding process follows from the observation that each of the products **20** and **22** is converted into the same enantiomeric form of the 1°-alcohol **23** (90%, 87% ee[15]) on reduction with lithium aluminium hydride. This outcome is fully consistent with the transition state structure expected to be involved[13] in the cyclisation of the iminium ion derived from **17**. In a similar manner the higher homologue of **17**, *viz*. compound **19**, cyclised in the presence of MacMillan's catalyst to give the expected product **24** in 75% yield and 96% ee. Disappointingly, the lower homologue of **17**, *viz*. compound **18**, failed to engage in the hoped-for cyclisation process. Reaction of the *N*-acyl-2-oxazolidinone **14** with the box ligand [Cu((*R*,*R*)-Bz-box)]-$(SbF_6)_2$[16] in hexafluoroisopropanol–dichloromethane at −78 °C for 2 h gave product **25** (94%) which upon reduction with lithium borohydride afforded alcohol **23** in 91% yield albeit in only 26% ee. In dramatic contrast, when the first step of the same sequence was carried out with the [Cu((*R*,*R*)-Ph-box)]$(SbF_6)_2$[16] ligand then *ent*-**25**, rather than **25**, was obtained in 95% yield and 88% ee.



The absolute stereochemistry of the cyclisation products **20**, **22**, **25** and *ent*-**25** was established through a chemical correlation study (Scheme 3) involving conversion of the last of these into an indolizidine-type natural product of known configuration. Thus, the enolate derived from *N*-acyl-2-oxazolidinone *ent*-**25** was reacted with the Davis oxaziridine[17] to give the α-hydroxylated derivative **26** as a *ca*. 1 : 1 mixture of diastereoisomers. Reduction of compound **26** with lithium borohydride then afforded the *vic*-diol **27** (63% from *ent*-**25**, 1 : 1 mixture of diastereoisomers) which was immediately



Scheme 3 *Reagents and conditions*: (i) Davis oxaziridine (1.1 mole eq.), NaHMDS (1.1 mole eq.), THF, −78 °C, 0.5 h; (ii) $LiBH_4$ (1.5 mole eq.), THF, 18 °C, 2 h; (iii) $NaIO_4$ (1.3 mole eq.), THF–pH 7 aq. buffer, 0 °C, 0.5 h then $NaBH_4$ (1.5 mole eq.), EtOH, 0 °C, 0.25 h; (iv) H_2 (4 atm.), 5% Rh on Al_2O_3 (5 w/w%), $(CF_3)_2CHOH$, 18 °C, 2 h.

cleaved with $NaIO_4$ in aqueous buffer. The resulting and highly sensitive aldehyde was immediately reduced, with $NaBH_4$, to the alcohol **28** (78% from **27**) which was obtained in 90% ee as determined by chiral HPLC analysis.[18] Hydrogenation of compound **28** at 4 atm using rhodium on alumina as catalyst and hexafluoroisopropanol as solvent then afforded a chromatographically separable mixture of (−)-tashiromine **29** {85%, $[a]_D$ −35 (*c* 0.87, $CHCl_3$), lit.[19a] $[a]_D$ −36.3 (*c* 0.88, $CHCl_3$)} and (−)-*epi*-tashiromine **30** {5%, $[a]_D$ −0.96 (*c* 0.31, ethanol), lit.[19b] $[a]_D$ (of enantiomer) +1.1 (ethanol)}. The NMR spectral data derived from compounds **29** and **30** were in excellent agreement with those reported[19c,d] in the literature.

Tanis and Raggon have previously shown[20] that pyrroles can act as effective terminators in epoxide-initiated cationic cyclisation sequences but, to date, no study involving enantiomerically enriched substrates appears to have been undertaken. Consequently, the final aspects of the present study involved examination of the indium trichloride-promoted[21] cyclisation of epoxy-alcohol **16**. In the event an 84% yield of compound *ent*-**27** (70% de) was obtained. Using the same protocol (oxidative cleavage/reductive work-up) as employed previously (Scheme 3), this diol was converted into the 8-hydroxymethyltetrahydroindolizidine *ent*-**28** (52% yield, 70% ee). These results suggest that the conversion **16**⟶**27** definitely does not proceed with strict inversion of configuration at the relevant carbon of the epoxide ring.

The foregoing results demonstrate that chiral substrates, auxiliaries and/or catalysts can all be employed in the preparation of enantiomerically enriched 8-substituted tetrahydroindolizidines, and higher homologues thereof, from pyrroles incorporating *N*-tethered Michael acceptors and other electrophiles. Our efforts are now focused on using such methods for the enantioselective construction of quaternary carbon centres as seen, for example, at C8 in compound **4**. Results will be reported in due course.

Acknowledgements

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15 This ee was determined using a Diacel AS-Chiralpak 46 × 250 mm column with 5 : 95 v/v isopropanol–hexane as the eluting solvent (flow rate of 0.7 ml min^{-1}); R_t (major enantiomer): 12.3 min; (minor enantiomer): 14.9 min.
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